

## **REMARKS**

Appreciation is hereby expressed to Examiner Sharmilla Gollamudi for the telephone interview so courteously granted on August 22, 2005. Pursuant to that interview, claims 11, 12 and 17 have been cancelled, and claim 1 has been amended as discussed with the Examiner. Support for the amendment of claim 1 can be found in the Specification on page 7, first paragraph, page 9, lines 11-13, page 19, line 9, lines 14-17, in Example 7, page 55, lines 5-19, and Example 36, page 56, lines 8-17. The present amendment is deemed not to introduce new matter. Claims 1, 8 and 13 remain in the application, Claim 13 having been withdrawn from consideration as being drawn to a non-elected invention.

Reconsideration is respectfully requested of the rejection of Claims 1, 8, 11-13, and 17 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As discussed during the interview, claim 1 has been amended herein to delete the objection “and/or” terminology referred to by the Examiner, and to now clearly state that “gelatin” is an optional element of the adhesive gel composition of claim 1. In view of the amendments to claim 1, and pursuant to the discussions during the interview, it is believed that this rejection is now moot. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of Claims 1, 8, 11-12, and 17 under 35 U.S.C. § 103(a) as being unpatentable over in view of Oda, et al. (5,725,874) in view of Linkwitz, et al.

The Oda, et al. reference, discloses a solubilizer and percutaneously absorbable external preparations containing same. However, as the Examiner has recognized, Oda, et al. fail to

disclose the combination of “1 to 20% by weight of lidocaine and 0.001 to 0.5% by weight of epinephrine, both in free form”, as claimed herein. Further, Oda, et al. fail to disclose a combination of sodium hydrogen sulfite and oxyquinoline, acting as antioxidants, as now claimed herein in amended claim 1. Moreover, as the Examiner has stated, Oda, et al. disclose using ascorbic acid as an antioxidant. However, combining only ascorbic acid (as the antioxidant) with epinephrine cause the color of the gel to be black, which is undesirable.

To cure the deficiencies of Oda, et al., as discussed above, the Examiner has cited Linkwitz, et al., to teach the combination of lidocaine and epinephrine. Linkwitz, et al. disclose a formulation for electrically assisted delivery of lidocaine and epinephrine. In particular, Linkwitz, et al. teach compositions containing lidocaine and epinephrine to be applied to a patient via iontophoresis, electroosmosis or electroporation. However, as with the cited Oda, et al. reference discussed above, Linkwitz, et al. fail to teach the now claimed combination of antioxidants (i.e., sodium hydrogen sulfite and oxyquinoline sulfate).

In contrast, the present invention, as claimed in amended claim 1 herein and as shown in Examples 35 and 26 on pages 55 and 56 of the instant application, provides a gel composition comprising *a combination of* 1 to 20% by weight of lidocaine and 0.001 to 0.5% by weight of epinephrine both in free form, a polyacrylic acid, a polyfunctional epoxy compound, water, polyhydric alcohol, sodium hydrogen sulfite and oxyquinoline sulfate, in a total weight ratio of 30:1 to 60:1, as antioxidants, and, optionally, gelatin, wherein the weight ratio of the drugs in free form to polyacrylic acid is in the range of 3:1 to 1:3.

Lidocaine and, particularly, epinephrine, decompose over time via oxidation. The present inventors unexpectedly discovered that by using the now claimed combination of antioxidants (to

minimize the decomposition of the lidocaine and epinephrine over time), together with the claimed weight % of combination of lidocaine and epinephrine in free form, an adhesive gel exhibiting superior stability over time could be obtained. In particular, the compositions, of Examples 35 and 36, as well as the compositions of Comparative Examples 24 and 25, were mixed and stirred with heating at 50°C until a uniform mixture was obtained, and a crosslinking agent was added at 40°. These 4 compositions were then plastered individually onto release-treated PET liners in a thickness of 1 mm. The PET liners containing each of the 4 adhesives (1 each from Examples 35 and 36, and 1 each from Comparative Examples 24 and 25) mentioned above were stored at 50°C for 4 weeks, and subsequently analyzed to determine the % of lidocaine and epinephrine remaining on the PET liner after storage at 50°C for 4 weeks .

As illustrated in Table 15 on page 58 of the Specification, it was unexpectedly discovered that the now claimed compositions of the present invention containing the claimed amount of lidocaine and epinephrine, along with the claimed amount of sodium hydrogen sulfite and oxyquinoline sulfate, retain substantially all of the epinephrine initially in the gel composition. It is believed that this particular claimed composition, or the stabilizing effect of said antioxidants on lidocaine and epinephrine, is disclosed or suggested in neither the Oda, et al. reference nor the Linkwitz, et al. reference.

Thus, in view of the amendments made herein, as well as the resulting deficiencies of the cited references as pointed out above, that the Examiner would be justified in no longer maintaining this rejection. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of Claims 1, 8, 12 and 17 under 35 U.S.C. §103(a) as being unpatentable over Oda, et al. (5,725,874) in view of Lugnani, et al.

(5,843,016).

The Oda, et al. reference is discussed in detail above. As the Examiner has recognized on page 5 of the instant Office Action, the Oda, et al. reference fails to teach the instant lidocaine and epinephrine combination. The Examiner has attempted to cure this deficiency by citing the Lugnani, et al. reference.

Lugnani, et al. disclose a method of treating acute urinary outflow system obstructions, comprising insertion of within the prostatic urethra and within the bladder cavity of a urethral catheter adapted to perform the electromotive administration of a drug or drug mixture into diseased prostatic tissues. Lugnani, et al. do, as the Examiner has stated, teach a combination of lidocaine and epinephrine. However, as with Oda, et al. Lugnani, et al. fail to teach or suggest the combination of elements now herein.

In particular, Lugnani, et al. fail to teach or suggest a gel composition comprising *a combination of* 1 to 20% by weight of lidocaine and 0.001 to 0.5% by weight of epinephrine both in free form, a polyacrylic acid, a polyfunctional epoxy compound, water, polyhydric alcohol, sodium hydrogen sulfite and oxyquinoline sulfate, in a total weight ratio of 30:1 to 60:1, as antioxidants, and, optionally, gelatin, wherein the weight ratio of the drugs in free form to polyacrylic acid is in the range of 3:1 to 1:3. Rather, that teaching comes only from the present invention, and constitutes an important element or aspect thereof.

In view of the showing of unexpected results discussed above, the amendments to claim 1 herein, and the deficiencies of the cited references pointed out above, it is believed that the Examiner would now be justified in withdrawing the rejection of remaining claims 1 and 8. Withdrawal of the rejection is accordingly respectfully requested.

Reconsideration is respectfully requested of the rejection of claim 11 under 35 U.S.C. 103(a) as being unpatentable over Oda, et al. (5,725,874) in view of Lugnani, et al. (5,843,016) in further view of JP 08-325149.

Although claim 11 has been cancelled herein, the undersigned wishes to address this rejection herein, with relation to claim 1. In particular, the undersigned respectfully points out that the cited secondary reference of JP 08-325149, like the other prior art of record, fails to disclose an adhesive gel composition for iontophoresis as now called for in amended Claim 1 herein.

In particular, JP 08-325149 fails to teach or suggest a gel composition comprising *a combination of* 1 to 20% by weight of lidocaine and 0.001 to 0.5% by weight of epinephrine both in free form, a polyacrylic acid, a polyfunctional epoxy compound, water, polyhydric alcohol, sodium hydrogen sulfite and oxyquinoline sulfate, in a total weight ratio of 30:1 to 60:1, as antioxidants, and, optionally, gelatin, wherein the weight ratio of the drugs in free form to polyacrylic acid is in the range of 3:1 to 1:3, and that unexpectedly superior stability characteristics could be obtained with said combination of elements. On the contrary, that teaching comes only from the present application and constitute an important element or aspect of the present invention.

As the Examiner has stated, the JP '149 reference discloses sodium hydrogen sulfite. However, sodium hydrogen sulfite is a so-called "reducing agent". As such, sodium hydrogen sulfite stabilizes other materials by being oxidized itself. Further, it is water soluble so as to have sufficient solubility in a hydrogel composition.

In contrast, the oxyquinoline sulfate of the present invention is a so-called "scavenger".

As such, oxyquinoline sulfate traps radicals existing in the system, and stabilizes same by resonance of the quinoline bone. Thus, the oxyquinoline sulfate of the present invention controls the chain production of radicals, and is easily solubilized in water and alcohols. For example, as shown in the specification herein, lidocaine and epinephrine are both stabilized in hydrogel compositions by using sodium hydrogen sulfite AND oxyquinoline sulfate IN COMBINATION.

In view of the foregoing, it is respectfully submitted that the claims now in the application are in condition for allowance, and early action and allowance thereof is accordingly respectfully requested. In the event there is any reason why the application cannot be allowed at the present time, it is respectfully requested that the Examiner contact the undersigned at the number listed below to resolve any problems.

Respectfully submitted,



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## CERTIFICATE OF MAILING

I hereby certify that this Amendment in Docket No. MUR-026-USA-PCT, Serial No. 09/831,879, filed May 22, 2001, was deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to:

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

On September 6, 2005.

Donald E. Townsend, Jr.

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